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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

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(54) Benzimidazole and Azabenzimi-Dazole Derivatives, Their Methods of Preparation, Synthesis Intermediates and Pharmaceutical Compositions in Which They Are Present and Which Are Useful Especially for the Treatment of Cardiovascular D seases and Duodenal Ulcers

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(57) 25 Claims

NO DRAWINGS

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IN THE C A N A D I A N PATENT AND TRADEMARK OFFICE

PATENT APPLICATION

entitled: Novel benzimidazole and azabenzimidazole derivatives, their methods of preparation, synthesis intermediates and pharmaceutical compositions in which they are present and which are useful especially for the treatment of cardiovascular diseases and duodenal ulcers

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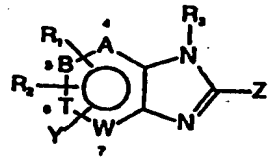
ABSTRACT OF THE DISCLOSURE

The present invention relates to the products of the formula



FORMULA (I)

and their tautomeric forms, in which formula:
- Y is located in the 4-, 5-, 6- or 7-position of the benzimidazole or azabenzimidazole ring and is an imidazole, benzimidazole, triazole or imidazothiazole deri-

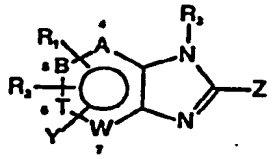
vative which is unsubstituted or substituted by groups such as halogen, COR_5, OR_5, SR_5, $COOR_5$ (R_5 being a hydrogen atom or a lower alkyl radical) or a lower alkyl radical which is unsubstituted or substituted by halogen, OR_5, SR_5, $COOR_5$, NHR_5, $NHCOR_5$ or COR_5 groups, R_5 being as defined above;

- Z can be a phenyl or pyridyl ring directly bonded to the benzimidazole or azabenzimidazole or indirectly bonded via a nitrogen atom which is unsubstituted or substituted by a lower alkyl radical, in particular aniline or aminopyridine, the phenyl or pyridyl ring being unsubstituted or substituted in particular by one or more lower alkyl radicals, one or more halogen atoms, one or more OR_5, SR_5, SOR_5, $NHCOR_5$ or NHR_5 groups (R_5 being as defined above) or a 5-membered to 10-membered heterocycle containing 1 to 3 heteroelements selected from nitrogen, oxygen and sulfur, or Z can also be an OH, SH, SR_5 or SOR_5 group, R_5 being a lower alkyl, a C_2-C_5 alkenyl, in particular an allyl, or a C_2-C_5 alkynyl, in particular a propargyl;
- R_1 and R_2 independently of one another are the hydrogen atom, a halogen atom, a CF_3, NO_2, NHR_4, $NHCOR_4$, OR_4 or SR_4 group (R_4 being a hydrogen atom or a lower alkyl radical) or a lower alkyl and can be located in the 4-, 5-, 6- or 7-position of the benzimidazole or azabenzimidazole;
- R_3 is the hydrogen atom and can be a lower alkyl radical or a benzyl group if Z is an OH, SH, SR_5 or SOR_5 group; and
- A, B, T and W can be a carbon atom or a heteroelement such as nitrogen,

and to the drugs in which they are present.

WHAT IS CLAIMED IS:

1. Benzimidazole and azabenzimidazole derivatives of the formula



FORMULA (I)

and their tautomeric forms, in which formula:
- Y is located in the 4-, 5-, 6- or 7-position of the benzimidazole or azabenzimidazole ring and is an imidazole, benzimidazole, triazole or imidazothiazole derivative which is unsubstituted or substituted by groups such as halogen, CORs, ORs, SRs, COORs (Rs being a hydrogen atom or a lower alkyl radical) or a lower alkyl radical which is unsubstituted or substituted by halogen, ORs, SRs, COORs, NHRs, NHCORs or CORs groups, Rs being as defined above;
- Z can be a phenyl or pyridyl ring directly bonded to the benzimidazole or azabenzimidazole or indirectly bonded via a nitrogen atom which is unsubstituted or substituted by a lower alkyl radical, in particular aniline or aminopyridine, the phenyl or pyridyl ring being unsubstituted or substituted in particular by one or more lower alkyl radicals, one or more halogen atoms, one or more ORs, SRs, SORs, NHCORs or NHRs groups (Rs being as defined above) or a 5-membered to 10-membered heterocycle containing 1 to 3 heteroelements selected from nitrogen, oxygen and sulfur, or Z can also be an OH, SH, SRs or SORs group, Rs being a lower alkyl, a C_2-Ce alkenyl, in particular an allyl, or a C_2-Ce alkynyl, in particular a

propargyl;

- R_1 and R_2 independently of one another are the hydrogen atom, a halogen atom, a CF_3, NO_2, NHR_4, $NHCOR_4$, OR_4 or SR_4 group (R_4 being a hydrogen atom or a lower alkyl radical) or a lower alkyl and can be located in the 4-, 5-, 6- or 7-position of the benzimidazole or azabenzimidazole;
- R_3 is the hydrogen atom and can be a lower alkyl radical or a benzyl group if Z is an OH, SH, SR_8 or SOR_8 group; and
- A, B, T and W can be a carbon atom or a heteroelement such as nitrogen,

and their addition salts with acids which are advantageously pharmacologically acceptable.

2. Derivatives according to claim 1 in which Y is imidazole.

3. Derivatives according to claim 1 or claim 2 in which Z is the pyridyl radical, in particular pyrid-4-yl.

4. Derivatives according to claim 1 or claim 2 in which Z is aminopyridine and in particular 4-aminopyridine.

5. Derivatives according to claim 1 or claim 2 in which Z is the OH group.

6. Derivatives according to claim 1 or claim 2 in which Z is the SH group.

7. Derivatives according to any one of claims 1 to 6 in which R_1 is hydrogen.

8. Derivatives according to any one of claims 1 to 6 in which R_1 is a C_1-C_8 lower alkyl radical, in particular methyl, preferably in the 6-position or 7-position.

9. Derivatives according to any one of claims 1 to 8 in which R_1 is the chlorine atom.

10. Derivatives according to any one of claims 1 to 6 in which R_1 is the trifluoromethyl group.

11. Derivatives according to any one of claims 1 to 10 in which R_2 is the hydrogen atom.

12. Derivatives according to any one of claims 1 to 10 in which R_2 is the methyl radical.

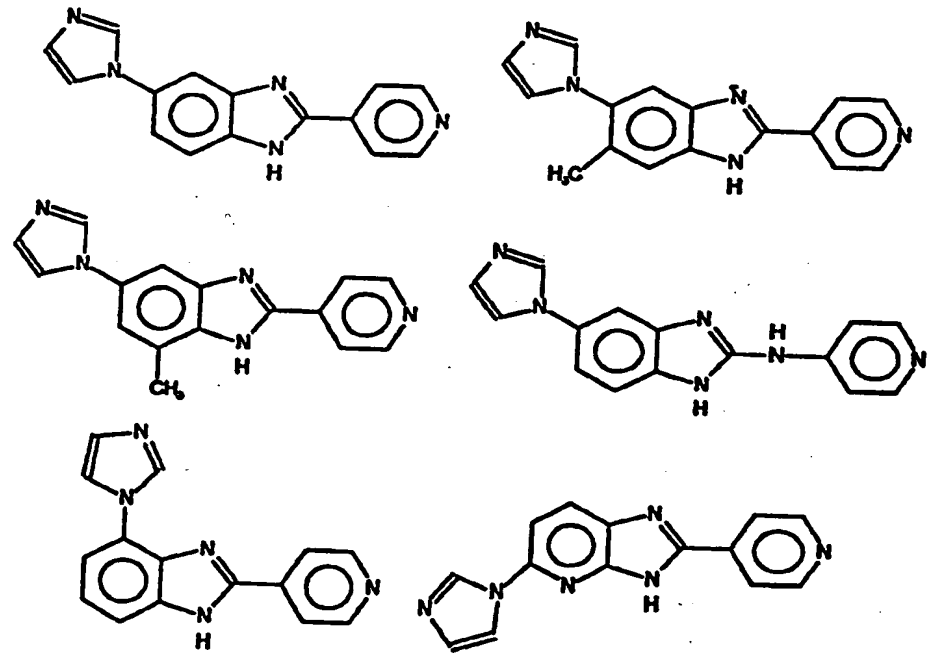
13. Derivatives according to any one of claims 1 to 12 in which R_3 is the isopropyl radical if Z is the OH or SH group.

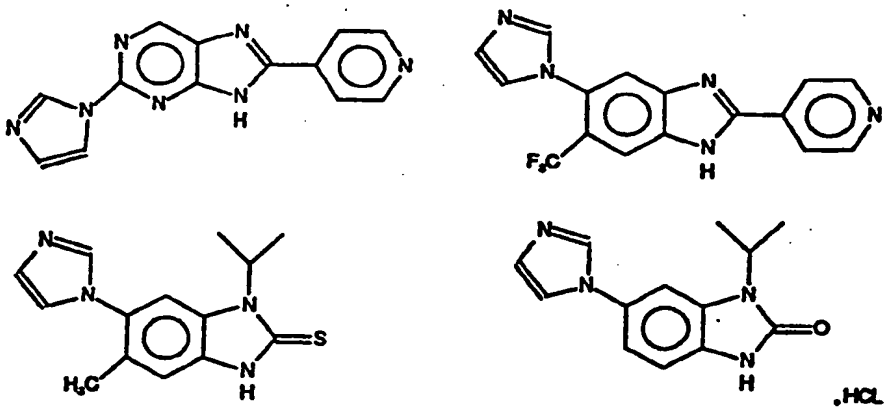
14. Derivatives according to any one of claims 1 to 13 in which W is the nitrogen atom.

15. Derivatives according to any one of claims 1 to 14 in which B and W are nitrogen atoms.

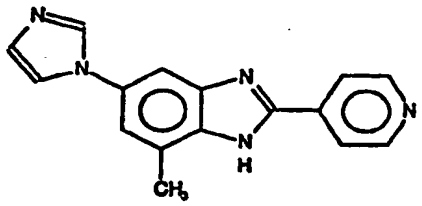
16. Derivatives according to any one of claims 1, 2, 3, 8, 11 and 13 to 15 in which R_1 is a lower alkyl radical, in particular methyl, in the 7-position, R_2 is the hydrogen atom, Y is an imidazolyl radical and Z is a pyrid-4-yl radical.

17. Derivatives according to any one of claims 1 to 16 which are selected from the products of the formulae

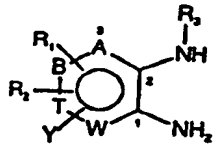




18. A novel benzimidazole derivative of the following structural chemical formula:



19. Methods of preparing the compounds of formula (I) according to any one of claims 1 to 18, which comprise preparing said compounds by reacting urea, thiourea, carbon disulfide, an aromatic or pyridine aldehyde (the reaction being followed by oxidation), an aromatic or pyridine acid chloride, a benzoic or pyridine acid, an aromatic or pyridine nitrile, an aromatic or pyridine dithiocarbamate, an aromatic or pyridine isothiocyanate or an aromatic or pyridine imidodithiocarbonate with diamino compounds of formula (II):



FORMULA (II)

in which:
R_1 and R_2 independently of one another are the hydrogen atom, a halogen atom, a CF_3, NO_2, NHR_4, $NHCOR_4$, OR_4 or SR_4 group (R_4 being a hydrogen atom or a lower alkyl radical) or a lower alkyl;
R_3 is the hydrogen atom, a lower alkyl or a benzyl group; and
Y is an imidazole, benzimidazole, triazole or imidazothiazole derivative which is unsubstituted or substituted by groups such as halogen, COR_5, OR_5, SR_5, $COOR_5$ (R_5 being a hydrogen atom or a lower alkyl radical) or a lower alkyl radical which is unsubstituted or substituted by halogen, OR_5, SR_5, $COOR_5$, NHR_5, $NHCOR_5$ or COR_5 groups, R_5 being as defined above.

20. Synthesis intermediates of formula (II) as defined in claim 19, which are useful for the preparation of the corresponding compounds (I) as defined in any one of claims 1 to 18.

21. A pharmaceutical composition which comprises a pharmaceutically effective amount of at least one compound of formula (I) as defined in any one of claims 1 to 18, or one of its addition salts with a pharmacologically acceptable acid, which may or may not be incorporated in a pharmaceutically acceptable excipient, vehicle or carrier.

22. A pharmaceutical composition with cardiovascular activity, which comprises a pharmaceutically effective

amount of at least one compound of formula (I) as defined in any one of claims 1 to 18, or one of its addition salts with a pharmacologically acceptable acid, which may or may not be incorporated in a pharmaceutically acceptable excipient, vehicle or carrier.

23. A pharmaceutical composition with secretion and/or ulcer inhibiting activity, which comprises a pharmaceutically effective amount of at least one compound of formula (I) as defined in any one of claims 1 to 18, which may or may not be incorporated in a pharmaceutically acceptable excipient, vehicle or carrier.

24. A method of preparing a therapeutic composition, which comprises incorporating a therapeutically effective amount of at least one compound of formula (I) as defined above in any one of claims 1 to 18, as well as its addition salts with pharmacologically acceptable acids if appropriate, into a pharmaceutically acceptable excipient, vehicle or carrier.

25. A method of preparation according to claim 24, wherein a pharmaceutical composition with cardiovascular, cardiotonic, vasodilative, antihypertensive and platelet aggregation inhibiting activity or secretion or ulcer inhibiting activity is prepared.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente